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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,846	06/24/1998	RICHARD P. WOYCHIK	CASE-03330	3529

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	21

DATE MAILED: 01/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/103,846	WOYCHIK ET AL.	
	Examiner	Art Unit	
	Joseph Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-12,14-22,24-26,28 and 35-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-12,14-22,24-26,28 and 35-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made.of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

Applicants' amendment filed September 20, 2001, paper number 20, has been received and entered. Claims 13, 27, 30, 31, 33 and 34 have been canceled. Claims 1, 15, 35 and 36 have been amended. Claims 37-50 have been added. Claims 1-8, 10-12, 14-22, 24-26, 28 and 35-50 are pending and currently under examination.

Oath/Declaration

The substitute declaration filed September 20, 2001, paper number 17, has been received and entered. The substitute declaration is in compliance with 37 CFR 1.67(a).

Specification

The disclosure is objected to because of the following informalities: The specification contains several references to a URL (for example: page 22; line 18). The attempt to incorporate subject matter into the patent application by reference to a hyperlink an/or other forms of browser-executable code is considered to be an improper incorporation by reference (See MPEP 608.01(p)).

Appropriate correction is required.

Claim Objections

Claims 42 and 45 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 42 is drawn to generating a transgenic mouse with two mutations in a gene of interest. This method simply uses the cells generated by the method of claim 37, and does not represent an additional step for producing an allelic series of cells as recited in the preamble of claim 37. Claim 45 is drawn to a means of detecting a mutation, however it is as an extra step after the isolation of a modified cell. Claim 45 seems to be directed to a particular method used in step c.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-8, 10-12, 14-22, 24-26, 28, 35 and 36 stand rejected and newly added claims 37-40, 42, 43, 46, 48 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Schafer *et al.*

Applicants indicate that Schafer *et al.* do not recite the embodiment encompassing the step of 'isolating' cells that contain the modified gene of interest. Applicants note that in the examples that a mixture of cells are used to generate mutagenized animals without any prior sorting or isolation. Applicants argue that because Schafer *et al.* do not teach the step of isolating, the claims can not be anticipated by the teachings. See Applicants' amendment, pages 11-12, bridging paragraph. Applicants' arguments have been fully considered but not found persuasive.

Newly added claims are drawn to producing an mixture of ES cells containing multiple different modifications in a gene of interest. Examiner would agree that examples provided by Schafer *et al.* do provide the guidance for using a mixture of mutagenized cells for the generation of a heterogenous population of mutant mice. However, a review of the work as a whole clearly indicates that for characterization of a mutant, individual mice must be analyzed. Further, Schafer *et al.* teach that alternatively, following DNA analysis for a mutation in a gene of interest, 'such as mutated ES clones in culture, the cells are transferred to the developing embryo' (see column 3; lines 4-61 and column 7; lines 3-6). Clearly, Schafer *et al.* anticipate identifying and characterizing the mutation in cells before further use, and not only the use of heterogenous mixtures of cells. Thus, Schafer *et al.* do teach the step of isolation. In addition, Schafer teaches the use of a mixture of cells for the generation of a genetically altered mouse, thus anticipates the methods directed to incorporating more than one variant into a mouse. As

such, the methods taught by Schafer *et al.* meet the limitations set forth in the instant claims, and therefore, the rejection is maintained.

Newly added claims 37-40, 43, 45, 46, 47 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Goodfellow *et al.*

Applicants point out that Goodfellow *et al.* do not teach conditions wherein 'at least one modification is produced in substantially every gene in said mouse embryonic stem cells' See Applicants' amendment, pages 12-13. Applicants' arguments have been fully considered but not found persuasive.

First, Examiner agrees that amendments to claims have obviated the basis of the rejection for claims 1-8, 10-12, 14-22, 24-26, 28, 35 and 36, and for these claims the rejection is withdrawn. However, Goodfellow *et al.* do teach the genetic alteration of a gene of interest in embryonic stem cells. Further, review of the general and specific methodology taught in Goodfellow *et al.* clearly overlaps with the conditions taught in the instant specification. Goodfellow *et al.* teach that the mutagenizing step should be done where about 1 mutation occurs in every 10,000-1,000 genes with the average in frequency of 1/500 and preferably 1/1000,-1/10,000 (column 4; lines 18-20 and lines 31-34). Additionally, Goodfellow *et al.* indicate that the art teaches that there may be 50-100,000 unique genes in development and 30,000 unique ESTs representing different genes. Finally, in the description of the invention Goodfellow *et al.* teach that the described methods can result in 5-15 independent and different protein alterations

can be generated among 10,000 organisms. Examiner would agree that Goodfellow *et al.* do not specifically recite that at least one modification in every gene is produced by the described methods, however in view of the teachings as a whole, Goodfellow *et al.* clearly set forth the limitations with respect to the number of possible genes, amount of mutagenizing required or optimized for, and expected amount of resulting mutants to indicate that at least one mutation in every gene is generated following the methods which are disclosed. As such, the methods taught by Goodfellow *et al.* meet the limitations set forth in the instant claims, and therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 10-12, 14-22, 24-26, 28, 35-40 and 42-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schafer *et al.*, Goodfellow *et al.* in view of either Kohler *et al.* (IDS reference JNCI, 1993) or Guay-Woodford *et al.* (IDS reference J. Int. Soc. Neph., 1996).

Claims 1-8, 10-12, 14-22, 24-26, 28, 35-40, 42, 43, 45-49 are summarized above. Claims 44 and 50 are directed to specific genes of interest consisting of p53, PKD family members and BRCA1. As indicated above, the combined teachings of Schafer *et al.* and Goodfellow *et al.* anticipate the claims 1-8, 10-12, 14-22, 24-26, 28, 35-40, 42, 43, 45-49. Briefly, both Schafer *et al.* and Goodfellow *et* al. teach methods of chemical mutagenesis of embryonic cells for identifying a mutation in a gene of interest. Each provide general and detailed guidance on the chemical properties of known mutagens and methods of using said mutagens for generating a mutation in a gene of interest. The general intended use of the methods is for the characterization of a gene of interest, however, Goodfellow *et al.* specifically teach that the disclosed methods of genetic modifications can be used to generate animal models of human diseases (column 8; lines 30-61). Each Schafer *et al.* and Goodfellow *et al.* teach that the methods can be used for any gene of interest and specifically Schafer *et al.* teach the alteration of c-kit and Goodfellow *et* al. teach the alteration of tyrosinase and Sry, however neither specifically teach the gene recited in claims 44 and 50. Kohler *et al.* teach two modifications of PKD and Guay-Woodford *et al.* teach a spectrum of mutations in p53. Each Kohler *et al.* and Guay-Woodford *et al.* discuss the characterization and implications of the mutations in their respective disease conditions. Further, each discuss the need to further analyze the effects and

consequences these mutations and other mutations with respect to the genetic linkage to their respective diseases. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the methods described by Schafer *et al.* and Goodfellow *et al.* for the genes of interest specifically taught in Kohler *et al.* or Guay-Woodford *et al.* One having ordinary skill in the art would have been motivated to pick p53 and PKD genes as genes of interest because of their implicated roles in human diseases and because of the need for further characterization in these diseases. There would have been a reasonable expectation of success to target p53 and PKD as genes of interest given the successful results of Schafer *et al.* and Goodfellow *et al.* for several other genes of interest, and the teachings of both Kohler *et al.* and Guay-Woodford *et al.* that specific mutations can be made and already exist and result in detectable phenotypic changes.

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed. Claim 41 is free of the art of record because the art fails to teach that as little as 200-600 ES cells could successfully be used in the recited methods. The closest teaching to this low range of cells as a starting material is by Schafer *et al.* who suggest that as few as 1000 organisms (i.e cells) could be used to obtain a single mutant copy of a gene (column 6; lines 45-54). In addition, Schafer *et al.* do teach as little as 300 mice can be used (Example 1:

column 14; lines 58-67), however in this example the spermatogonia are the target cells, and thus, represent many more cells as starting material than 300 cells, and therefore would be outside the range of 200-600 cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached at (703)305-4081.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Kay Pickney whose telephone number is (703)306-3076.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Deborah Crouch

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